REMARKS/ARGUMENTS

By the present proposed amendment, four (4) claims are amended, zero (0) claims are cancelled, and four (4) new claims are added. No fees for claims are believed payable.

Support for amended claim 1 can be found in the specification as filed at least on page 13, line 6, page 21, line 10, and page 45, line 25 – page 46, line 1.

Support for amended claim 13 can be found in the specification as filed at least on page 45, line 25 – page 46, line 1.

Support for new claim 27 can be found in the specification as filed on page 12, line 13.

Support for new claims 28 – 30 can be found in the specification as filed at least on page 13, lines 15 – 24.

No new matter has been added by the present proposed claim amendments and no change in inventorship is believed to result. Entry of the proposed amendments is respectfully requested.

I. Rejection Under 35 U.S.C. § 112, first paragraph – Written Description Rejection.

Claims 1-5, 7, 13, 15-19 and 22-24 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

Applicants propose to amend the claims solely to expedite prosecution of certain embodiments of the present invention. Specifically, Applicants' proposed claim amendments make clear that "the protein fragment or peptide is GAD2 represented by SEQ. ID NO. 4" which, as is clearly defined in the specification, corresponds to amino acids 206-220 of GAD 65. (See at least page 45, line 20 – page 46, line 1 which defines GAD 2 as SEQ. ID NO. 4 corresponding to amino acids 206-220 of GAD 65). Withdrawal of this rejection is therefore respectfully requested.

II. Rejection under 35 U.S.C. § 112, first paragraph – Utility Rejection.

Claims 1-5, 7, 13, 15-19 and 22-26 stand rejected under 35 U.S.C. § 112, first paragraph on the alleged basis that there is "insufficient evidence that the claimed method could effectively

function as a method for suspending, preventing or delaying the onset of type 1 diabetes (IDDM)." OA at 3. Thus, the instant rejection is a utility rejection under 35 U.S.C. § 112, first paragraph grounded on the basis that the asserted utility is credible. Applicants respectfully traverse this rejection.

The MPEP states that "[o]ffice personnel should not impose a 35 U.S.C. 112, first paragraph rejection grounded on a 'lack of utility' basis **unless** a 35 U.S.C. 101 rejection is proper." MPEP 2164.07 IA and MPEP 2107.01 IV. (emphasis added). In particular, the factual showing needed to impose a rejection under 35 U.S.C. 101 must be provided if a 35 U.S.C. 112, first paragraph, rejection is to be imposed on 'lack of utility' grounds. *Id.*

As will be discussed in detail below, since the factual showing needed to impose a rejection under 35 U.S.C. 101 has ***not*** been made, the 35 U.S.C. 112, first paragraph, rejection must also fail.

1. A specific, substantial and credible utility has been established.

Applicants have asserted a specific, substantial and credible utility clearly meeting the utility requirements of 35 U.S.C. 101. Since a 35 U.S.C. 101 rejection is not proper, neither is a 35 U.S.C. 112, first paragraph rejection grounded on 'lack of utility' proper.

A. Specific Utility.

MPEP 2107.I.A provides that "[a] 'specific utility' is specific to the subject matter claimed and can 'provide a well-defined and particular benefit to the public'." Applicants have met this burden by, *inter alia*, asserting a method of preventing or delaying onset of type 1 diabetes in a subject in need thereof. This utility is specific to the subject matter claimed and clearly provides a well-defined and particular benefit to the public—prevention or delay of onset of type 1 diabetes. MPEP 2107.01I.A.

B. Substantial Utility.

MPEP 2107.01.I.B makes clear that to satisfy the "substantial utility" requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. Applicants submit that they have met this burden by, *inter alia*, asserting a method of preventing or delaying type 1 diabetes in a subject in need thereof—a significant, immediate and well-defined public benefit to be sure. "Courts have repeatedly found that the mere identification of a pharmacologic activity of a compound that is relevant to an asserted

pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." MPEP 2107.01 III (emphasis in original).

C. Credible Utility.

The Office Action suggests that because the claimed composition has not yet been shown to prevent or delay the onset of diabetes in humans that the utility is not credible. In particular, at page 3, the Office Action states that "[s]pecifically, the specification provides insufficient evidence that the claimed method could effectively function as a method for suspending, preventing or delaying the onset of type 1 diabetes (IDDM)". The Office Action further states that "it appears that the only actual evidence of record supports the position that the results of therapies in animal models cannot be used to predict the results of the same therapies in humans." OA at 6.

As an initial matter, Applicants point out that many of the claims are not limited to treatment of humans. As such, the Examiner's position that success in an animal model does not necessarily translate to success in humans is irrelevant with respect to such claims. Furthermore, the MPEP makes clear that "[c]redibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (*e.g.*, test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement." MPEP 2107II(B)(1)(ii). Importantly, proof of efficacy in humans is **not** a requirement for credible therapeutic utility in humans. MPEP 2107VI.

Moreover, the Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs marketed in the United States. MPEP 2107.01 III.

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott [v. Finney]*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [Fed. Cir. 1994)] Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating the incentive to pursue, through research and

> development, potential cures in many crucial areas such as the treatment of cancer.
>
> MPEP 2107.01 III (citing *In re Brana,* 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995)).

The MPEP goes on to state that these general principles are equally applicable to the situations where an applicant has claimed a process for treating a human or animal disorder. *Id.*

Furthermore, the MPEP states:

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof ***almost invariably*** will be sufficient to establish therapeutic or pharmacologic utility for a compound, composition or process. A cursory review of cases involving therapeutic inventions where 35 U.S.C. 101 was the dispositive issue illustrates the fact that the Federal Courts are not particularly receptive to rejections under 35 U.S.C. 101 based on inoperability. Most striking is the fact that in those cases where an applicant supplied a reasonable evidentiary showing supporting an asserted therapeutic utility, almost uniformly the 35 U.S.C. 101-based rejection was reversed...Only in those cases where applicant was unable to come forward with ***any*** evidence to rebut a finding by the Office that the claimed invention was inoperative was a 35 U.S.C. 101 rejection affirmed by the court...MPEP 2107.03.

Importantly, evidence does not even have to be in the form of data from an art-recognized animal model for the particular disease or condition to which the asserted utility relates. Rather, data from any test that the applicant reasonably correlates to the asserted utility should be evaluated substantively. MPEP 2107.03 III. If one skilled in the art would accept the animal tests as being reasonably predictive of utility in humans, evidence from those tests should be considered sufficient to support the credibility of the asserted utility. MPEP 2107.07 III.

In the present case, Applicants previously have submitted data from the NOD mouse model showing that the presently claimed method resulted in (a) protection of pre-diabetic mice from becoming diabetic and (b) restoration of normoglycemia in all mice tested. (See Declaration of co-inventor Dr. Habib Zaghouani dated December 19, 2007, already of record). Not only is the NOD mouse model an art-recognized animal model for type 1 diabetes, but it has been characterized by Baxter and Duckworth (previously submitted) at page 452 as "the most

characterized and best-validated model of autoimmune diabetes; it is the **gold standard** for modeling aetiologic, immunological, pathological and genetic aspects of the disease" (emphasis added). Therefore, direct evidence of record supports a reasonable correlation between the evidence of utility of record and the disease to which the asserted utility relates (type 1 diabetes).

The Office Action states that "it appears that the only actual evidence of record supports the position that results of therapies in animal models cannot be used to predict the results of the same therapies in humans." OA at 6. Applicants respectfully disagree with this conclusion. First, as discussed in detail above, evidence of efficacy in humans is not required. Second, the utility requirement only requires a reasonable correlation between the activity in question and the asserted utility, not absolute certainty.

i. Couzin does not evidence failure of the NOD model to predict success in humans.

The Office Action points to a post-filing date lay paper by Couzin allegedly disclosing two failed attempts to treat human diabetes by administering insulin (oral and injected). As an initial matter, Applicants note that there is a significant difference between the apparent approach and compounds administered in studies discussed in that paper and the instant claims. Further, the Office Action characterizes Couzin as describing attempts to induce "tolerance to insulin." OA at 5. No indication is found in Couzin that the researchers were in fact attempting to induce "tolerance to insulin." Rather, the article suggests that insulin was selected because it was thought insulin could boost the number of T cells or that reducing glucose levels by supplying insulin lessened the stress on beta cells. Couzin at 1863, Col. 2. Therefore these alleged failed attempts to not appear to reflect failed attempts at inducing tolerance as characterized in the Office Action.

Notwithstanding the foregoing, the Office Action states that "both oral and injected forms of insulin could be used to induce tolerance in the NOD mouse", but subsequently failed in humans. OA at 5. Applicants note that at page 1863 Couzin indicates that earlier "rodent" and "preliminary human date" had suggested that it (injected insulin) could ***prevent*** diabetes. It is unclear from that passage whether the rodent model in question was the NOD model, whether tolerance to insulin was in fact induced and if so what the mechanism for oral and injected tolerance might have been. If additional evidence regarding the NOD model appears in Couzin, Applicants were unable to find it and respectfully request a citation to the appropriate page and

line. Moreover, even if the underlying studies discussed in Couzin were performed in NOD mice, that would appear to be even further evidence that the researches believed there was a "reasonable correlation" between the NOD model and type 1 diabetes in humans, even if oral or injected insulin treatment did not end up working in humans.

ii. Harrison touts the NOD mouse model's ability to predict success in humans.

The Office Action further quotes the following statement in Harrison's abstract as evidence that the NOD model is not predictive of therapy in humans: "This strategy [negative vaccination] is therapeutically effective in inbred rodent models but its translation in humans has failed to meet expectations." The Office Action, however, critically omits the sentence which immediately follows the quoted sentence that states: "This failure can be attributed to the use of suboptimal dosage regimens in end-stage disease, as well as other factors." Thus, Harrison's statement was not intended as an indictment of the NOD model itself or its predictive value in humans, but rather of the dosing and timing (end stage disease) of the studies being referred to. In fact, Harrison goes on to state that:

> ...the spontaneously diabetic non-obese diabetic mouse, which mimics human type 1 diabetes in many ways, ***has provided 'proof of concept' for negative vaccination***. Recent trials of a nasal insulin vaccine in humans at risk of type 1 diabetes ***provide evidence of tolerance induction as a basis for clinical efficacy***." (Harrison Abstract; emphasis added).

Harrison further states that:

> A prerequisite for development of a human therapeutic is demonstrable efficacy and safety in animal models. The NOD mouse has greatly contributed not only to our understanding of disease mechanisms but to the expectation that T1D is preventable. Autoimmune diabetes in the NOD mouse shares features with human T1D, including polygenic inheritance dominated by genes for antigen presenting molecules in the MHC, autoimmune response to (pro) insulin and GAD65, transfer of disease by bone marrow and a protracted pre-clinical phase. NOD mice respond to many immune and other interventions, but most of these prevent disease in only a proportion of mice, others only retard disease onset and some have no effect (and therefore are not reported). ***The NOD mouse has provided 'proof of concept' for islet-antigen-specific vaccination strategies, as a basis for human***

> ***trials to prevent T1D***. (Harrison, p.141., emphasis added; internal citations omitted)

Thus, according to the Harrison reference (relied on by the Office for the proposition that results in animal models can't be used to predict results in humans), results in the NOD model actually provide proof of concept that form the very basis for moving forward with human trials.

Lastly, Applicants expressly disagree with the Examiner's comments in the second paragraph at page 6 of the Office Action. In the Office Action dated August 24, 2007, the Office stated, in the context of a 35 U.S.C. 112, first paragraph utility rejection, that at the time prior to the instant application's filing date and based on the Legge 1998 publication "it is just as likely that the method of the instant claims would exacerbate disease as treat or prevent it." OA dated 08/24/2007, page 6. Applicants argued, in response to an obviousness rejection in that same Office Action, that this unpredictability was evidence of non-obviousness. (OA response dated 12/19/2007, page 12). The Office somehow attempts to interpret Applicant's argument as an agreement with the Office that the instant claims are not enabled by the instant specification. Applicants expressly traverse this conclusion as factually and legally misguided. The results of the presently claimed methods were unpredictable ***prior to*** Applicants' invention. However, Applicants enabled the present claims via filing of the instant patent application and priority documents thereto. These are two different inquiries altogether focusing on different timeframes and different legal frameworks.

Conclusion:

Applicants respectfully submit that they have more then met the burden of providing specific, substantial and credible utility for the presently claimed invention. The evidence of record (e.g. Harrison and Baxter) strongly supports the fact that the NOD mouse is the gold standard model for type 1 diabetes and is used as a basis for human clinical trials. Since a 35 U.S.C. 101 lack of utility rejection cannot be sustained, nor is a utility rejection under 35 U.S.C. 112 proper. Withdrawal if the instant 35 U.S.C. 112 utility rejection is therefore requested.

III. Rejection Under 35 U.S.C. 103.

Claims 1-5, 7, 13, 15-19 and 22-26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/30706 in view of Kaufman et al., J. Clin. Invest. Vol. 89 pp. 283-292 (1992) ("Kaufman"). Applicants respectfully traverse this rejection.

1. No *prima facie* case established.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. *See, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); *Abbott Laboratories v. Sandoz, Inc.*, 529 F.Supp. 2d 893 (N.D. Ill. 2007) and MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, *e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that "a court ***must*** ask whether the improvement ***is more than*** the predictable use of prior art elements according to their established functions." *KSR* at 1740 (emphasis added). As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that a reasonable expectation of success existed. MPEP 2143.02.

As will be discussed in detail below, Applicants respectfully submit that in the instant case, no articulation of the reasons why the claimed invention would have been obvious has been established with respect to the claims, no reasonable expectation of success existed at the time the instant application was filed, and each and every claim limitation is not disclosed in the prior art. As such, the asserted *prima facie* case of obviousness fails.

According to the office action, WO 98/30706 teaches the treatment of autoimmune disorders employing a humanized IgG2b chimeric protein wherein an autoantigen peptide is inserted into the D segment of a CDR3 loop. OA at 7. WO 98/30706 is silent as to GAD65, GAD1 and GAD2. Kaufman, on the other hand, is cited for its disclosure that GAD65 and GAD67 may be involved in IDDM via molecular mimicry with the coxsackievirus. Kaufman is silent as to GAD1 and GAD2.

A. No articulated reasoning supports the asserted obviousness rejection.

The Office Action indicates that one of ordinary skill in the art would have been motivated to select GAD65 as the autoantigen for use in the claimed invention given the teachings of Kaufman. As an initial matter, the claim amendments proposed herein define the protein fragment or peptide as "GAD2 represented by SEQ. ID NO 4." SEQ. ID NO 4 is not

specifically taught or disclosed in Kaufman or WO 98/30706, nor is there any articulated reasoning in the record that would have led one of ordinary skill in the art to modify WO 98/30706 so as to select SEQ ID NO 4 over any other peptide or fragment thereof derived from GAD65 or GAD67 or any other suspected diabetic autoantigen protein for that matter. Absent such articulated reasoning, no *prima facie* case of obviousness has been established.

The Office Action further states that the teachings of Kaufman "indicate that GAD65 was one of the few known IDDM autoantigens at the time of the invention." OA at 7. Applicant respectfully disagrees with this conclusion. Kaufman was published in 1992 whereas the instant application has an earliest claimed priority date of April 9, 2002. Therefore, Kaufman is not necessarily indicative of the state of known IDDM autoantigens nearly a decade after Kaufman's publication date. Applicants respectfully point out that many potential diabetes autoantigens were known or suspected as of the filing date of the instant invention including, without limitation, islet cell autoantigen 69, glutamic acid decarboxylase, islet tyrosine phosphatase ICA512/IA-2, heat shock protein 60, carboxypeptidase H, 38-kDa protein, peripherin, and gangliosides (*e.g.* GM 2-1 and GM3), *etc.* In addition to the proteins themselves, there are numerous possible peptides and fragments of the foregoing. Applicants submit that there is no articulated rationale in the record as to why a person of ordinary skill in the art would have, at the time the present invention was made, selected SEQ ID NO. 4 from among the numerous potential type 1 diabetes autoantigen peptides and protein fragments and combined it with the construct of WO 98/30706. As such, no *prima facie* case of obviousness exists.

The Office Action further states that "[r]egarding timing of administration of the Ig-fusion protein set forth in claims such as 3, 16, 17, etc., said timing would comprise only routine optimization which would fall well within the purview of one of skill in the art at the time of the invention." OA at 7. Applicants respectfully disagree with this statement as conclusory and unsupported by any evidence or rationale. According to the MPEP, the mere statement that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish a *prima facie* case of obviousness without some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. MPEP 2143.01IV. No such articulated reasoning with rational underpinning has been provided to support the Office's conclusion. As such, no *prima facie* case of obviousness has been established.

For at least the foregoing reasons, withdrawal of the instant rejection is therefore respectfully requested.

B. No reasonable expectation of success.

Even if one of ordinary skill in the art would have had some reason combine SEQ. ID NO. 4 with the construct of WO 98/30706 to prevent or delay the onset of type 1 diabetes, which is not admitted, such a person would not have had a reasonable expectation of success in preventing or delaying the onset of type 1 diabetes, particularly in a subject that had undergone insulin autoantibody seroconversion.

The Office Action relies on WO 98/30706 which discloses a fusion protein having the proteolipid protein (PLP) autoantigen inserted into the D segment of a CDR3 loop. PLP is an autoantigen associated with multiple sclerosis. Applicants respectfully submit that the multiple sclerosis test model used in WO 98/30706 (experimental allergic encephalomyelitis) is far different from the type 1 diabetes NOD mouse model used in examples within the instant application such that any success or failure shown in WO 98/30706 would not be at all predictive of success or failure of an Ig-GAD2 fusion protein in prevention or delay of type 1 diabetes as presently claimed.

Specifically, the relevant examples in WO 98/30706 (*e.g.* Examples I and XI) involve induction of an immune response with a known pathogenic peptide (PLP1) followed by treatment of the induced immune response with a slightly altered version of the very same peptide (PLP-LR) introduced in the form of a chimeric antibody immunomodulating agent. PLP-LR is an analog of PLP1 in which Trp144 and His147 are replaced with Leu and Arg, respectively. Therefore, in Examples I and XI of WO 98/30706, a disease state is induced with a known pathogenic peptide and then treated with a slightly altered non-pathogenic version of the very same peptide.

In stark contrast to those examples, the onset of type 1 diabetes in the NOD mouse model is a *spontaneous* event not triggered by administration of a known peptide antigen. Because no inducer peptide is known, it was completely unpredictable at the time the present invention was made which peptide antigen, if any, when incorporated into compositions disclosed in the instant application, would have any impact on type 1 diabetes, let alone delay or prevent that disease state. This is very different from the situation in WO 98/30706 in which the disease inducing peptide was known at the outset, and treatment was provided with a slight variation of the very

same inducer peptide. In view of these significant differences and the highly unpredictable area of art of the presently claimed invention, a person of ordinary skill in the art at the time the present invention was made would not have had a reasonable expectation of success in delaying or preventing type 1 diabetes according to the presently claimed methods. Applicants respectfully submit that the outcome of the presently claimed methods was highly unpredictable at the time the present invention was made.

Furthermore, one of ordinary skill in the art at the time the present invention was made would not have had a reasonable expectation that SEQ ID NO 4, selected from the numerous type 1 diabetes autoantigen peptides and protein fragments known or suspected at the time, would prevent or inhibit diabetes as presently claimed. There is no articulated rationale in the record for selection of any particular diabetogenic peptide or protein fragment, nor any indication why a person of ordinary skill in the art would have had a reasonable expectation of delaying or preventing type 1 diabetes in an IAA positive subject with any such peptide or protein fragment.

Finally, the Office Action states that "the ordinary skilled artisan would likely have developed a treatment employing a combination of unaltered and altered GAD peptides to avoid the problems that might have occurred due to the administration of individual peptides. Employing this strategy the ordinary skilled artisan would have had every expectation of success in developing an effective treatment." Firstly, as is discussed above, no such expectation would have existed given the fundamental differences between the experimental allergic encephalomyelitis and NOD models. Secondly, the presently claimed invention does not require use of a combination of unaltered and altered GAD peptides. Therefore, based on the Office's interpretation of WO 98/30706, that reference actually teaches away from the presently claimed invention.

For at least the foregoing reasons, a person of ordinary skill in the art would not have had a reasonable expectation of success of preventing or delaying the onset of diabetes according to the presently claimed methods. Withdrawal of the instant rejection is therefore respectfully requested.

C. Each and every claim limitation not disclosed in the prior art.

As amended herein, claim 1 and all claims depending there from specify that "the subject has undergone insulin autoantibody seroconversion prior to the administering step." This limitation is simply not disclosed in the prior art of record. Nor is SEQ ID NO. 4 disclosed in the

prior art of record. Because the prior art when combined does not teach each and every limitation of the instantly claimed invention, the asserted *prima facie* case of obviousness fails.

Conclusion:

Applicants respectfully submit that in the instant case, no articulated reason why the presently claimed invention would have been obvious has been established, no reasonable expectation of success existed at the time the instant application was filed, and each and every claim limitation is not disclosed in the prior art. As such, Applicants respectfully submit that the asserted *prima facie* case of obviousness fails.

IV. Obviousness Type Double Patenting Rejection.

Claims 1-5, 7, 13, 15-19 and 22-26 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-7 and 13-16 of U.S. Serial N0. 11/290,070 and claims 1-7 and 13-16 of U.S. 11/425,084. Applicants will address these provisional rejections upon resolution of the outstanding non-provisional rejections.

CONCLUSION

The application is believed to be in condition for allowance. Early and favorable considerations is respectfully requested. The Commissioner is hereby authorized to charge deposit account 02-1818 for any fees which are due and owing.

Respectfully submitted,

BELL, BOYD & LLOYD LLP

BY 

David B. Fournier
Reg. No. 51,696
Customer No. 24573

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